REMARKS

Claims 1 to 48 were replaced by claims 1 to 49. More particularly, claims 1, 2, 12, 15, 16, 18, 20, 21, 32, 43, 46 and 47 were replaced by amended claims 1, 2, 12, 15, 16, 18, 20, 21, 32, 43, 46 and 47. A new claim 49 has been introduced.

Also, clerical errors appearing in pages 2 and 16 of the disclosure have been corrected as requested. New claim 49 does not introduce new matter. Support can be found in pages 14 (l. 30), 15 (l. 16, 23) and 16 (l. 10, 14).

Section V.

In paragraph V, the Examiner rejects claims 1-7, 9-16, 18-27, 29-38 and 40 to 47 for lack of novelty under provisions of Article 33(2) of the PCT in view of what is described in documents **D1 (WO 02/079183), D2 (WO 01/24824), D3 (WO 96/07431), D4 (US 5 773 460), D5 (GUIMOND et al.), D6 (CHEN et al.) and D7 (BRASSEUR et al.)**; and rejects claims 1 to 48 for lack of inventiveness under provisions of Articles 33(2) and (33(3) of the PCT in view of the teaching of documents **D1 (WO 02/079183), D2 (WO 01/24824), D3 (WO 96/07431) and D4 (US 5 773 460)**.

In paragraph V-2, the Examiner indicated in his written opinion that said documents D1 to D7 can be summarized as follows:

- **D1** discloses the production of rhodamine derivatives (including TH9402) that function as photosensitizers, and which preferentially localize in immunoreactive cells, where these cells can be subsequently destroyed by exposing them to visible light (PDT). The treatment may be in conjunction with an acceptable pharmaceutical carrier for the ex vivo elimination of reactive immune cells in patients with immunologic disorders. These rhodamines were found to be effective in preventing graft-versus-host disease (GVHD), and in the treatment of infections caused by Gram+ and/or Gram- bacteria, viral infections, leukemias, multiple myelomas and lymphomas, and solid tumors.

- **D2** discloses photoactivatable pharmaceutical compositions for the selective destruction of immunoreactive cells by using PDT in conjunction with a rhodamine derivative as photosensitizer (including TH9402). This was accomplished ex vivo, for the treatment of immunologic disorders, GVHD and organ rejection.

- **D3** discloses the synthesis of photosensitive rhodamine derivatives that are useful in PDT. Also disclosed is the preferential localization of these compounds in malignant cells, and their use in the treatment of tumors and in bone marrow purging for autologous transplantation.

- **D4** discloses photoactivatable rhodamine derivatives, including some of those encompassed by the present claims, for use in PDT. These derivatives were found to be preferentially localized in malignant cells, which lead to the selective destruction of these cells and lead to the in vitro treatment of tumors via the purging of cancerous clones in the bone marrow of chronic myelogenous leukemia (CML) patients.

- **D5** discloses that PDT of TH9402-exposed T-cells led to the selective elimination of immunoreactive T-cell populations, and determined that this can be applied to in the treatment of GVHD and other alloimmune and autoimmune disorders.

- **D6** discloses that mice injected with irradiated allologous spleen cells previously treated with TH9402 and exposed to visible light at 514 nm (photodynamic cell purging or PDP) allowed 90% of the recipients to remain tumor-free and free of GVHD for a 100 day observation period, and yet graft-versus-leukemia (GVL) activity is not impaired.

- **D7** discloses the use of the photosensitizer TH9402 and visible light in the PDT-mediated selective elimination of CML and breast cancer cells.

In paragraph V-3, the Examiner motivates his rejection as follows:

- Concerning claims 1, 2 and 32, the Examiner considers that each document **D1** to **D7** teaches the use of one or more of the rhodamine derivatives of the present claims for photodynamic therapy (PDT). More particularly, the Examiner considers that because after treatment of the cells, they are readministered to the patient, this can be seen as qualifying as use as a vaccine.

  In this regard, the Applicants wish to point out to the Examiner's attention that claims 1 and 2 are directed toward a new use of a medicament and claim 32 is directed toward a method for the preparation of a medicament. Also, the Applicants wish to point out to the Examiner's attention that prior art treatment involved the use of chemotherapy and radiation in association with PDT treatment of the graft. Patients underwent allogeneic or autologous stem cell transplantation because of underlying malignancy or immunologic disorder and the photodynamic purging strategy was used to eliminate either (1) malignant cells in autologous grafts, (2) immunologically active cells from patients with immunologic disorders (such as lupus erythematosus, scleroderma, etc.) from autologous grafts, or (3) alloreactive T cells in allogeneic grafts. Also cells obtained for graft purposes are a leukopheresis procedure that collects progenitors, while according to the current patent application, the cells collected are from a different fraction of cells representing the lymphocyte population.

  Also, in the prior art, the injection of cells was performed only one time while according to a particularly preferred aspect of the current patent application the injection can be repetitive. The prior art identified the elimination of cells as the treatment, while a particularly preferred

current approach according to the present invention requires cells to be reinfused, even if they are dead.

Therefore, according to the present invention said cells must not be removed by lavages or other strategies but are an intrinsic part of the treatment. In this regard, the Applicants wish to point out to the Examiner's attention that according to prior art it is customary to use strategies to eliminate cells that are destroyed after the purging procedure before infusing these cell products into the patient (cells are usually washed to remove dead cells, debris and substances that could be produced by cells that are reacting to PDT). In fact, several washing steps are included in all purging strategies, including all PDT treatment clinical trials that performed to date. In contrast, the Examiner will note that according to the present patent application it is exactly what would be removed that actually represents the active component of the treatment.

Also, the Examiner will note that the present modality can be used to induce an effect with other cells, for example the vaccine can consist of dendritic cells that were exposed to PDT treated cells or supernatant, and not the cells themselves. According to the present patent application, the activity can also rest in the supernatant of the treated cells, as aspect that was also not considered in the prior art since the supernatant was actually washed. In fact, the supernatant of cells treated by PDT in the previous application was removed from the graft prior to administration to the patient.

Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims 1, 2 and 32 in view of Documents **D1** to **D7** be withdrawn.

- Concerning claims 3, 4 and 33 to 35, the Examiner considers that documents **D1, D2, D5** and **D6** disclose the use of a PDT-cell medicament in the treatment of alloimmune and/or autoimmune disorders and GVHD and/or organ rejection. In this regard, the Examiner will note that in D1, D2, D5 and D6, the activity resided in the elimination of activated T cells, and the reinfusion of resting cells, without the immunoreactive T cells. However, the Applicants wish to point out to the Examiner's attention that in contrast, the present patent application indicates that the effect is mediated by the infusion of cells that are dying and would be removed by the lavages customarily performed before the infusion to the patient in prior art patents or publications. Also, the Examiner will note that even if diseases treated are indeed the same as in D1, D2, D5 and D6, the treatment is not in association with chemotherapy and / or radiation associated with transplantation. Also, the Examiner will note that D5 and D6 are documents on the prevention of GVHD, not treatment of auto-immune disorder that is already installed or active.

Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims 3, 4 and 33 to 35 in view of Documents **D1, D2, D5** and **D6** be withdrawn.

- Concerning claims 5 and 36, the Examiner considers that documents **D1** and **D2** disclose some of the claimed immunologic disorders. In this regard, the Applicants wish to point out to the Examiner's attention that even though the diseases targeted are the same as in D1 and D2, as previously mentioned in aforesaid item, the treatment according to the present patent application is different.

  Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims 5 and 36 in view of Documents **D1** and **D2** be withdrawn.

- Concerning claims 6, 7, 37 and 38, the Examiner considers that document **D1** discloses the infectious or viral source. In this regard, the Applicants wish to point out to the Examiner's attention that D1 disclosed that PDT eliminates infectious or viral source, not the treatment of such an infection by the injection of cells or infectious agents that are treated by PDT. More particularly, the Examiner will note that in D1, infectious or viral source was again washed away after PDT treatment. Quite this opposite the agents exposed to the PDT now become the active agent.

  Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims 6, 7, 37 and 38 in view of Document **D1** be withdrawn.

  Concerning claims 9 to 11 and 40 to 42, the Examiner considers that each of documents **D1**, **D3, D4** and **D7** discloses PDT-therapy with identical rhodamine derivatives for use in the treatment of at least one of the cancers defined in said claims. The Applicants wish to point out to the Examiner's attention that they agree that the diseases targeted are the same as those in the documents mentioned above. However, the Examiner will note that the method of treatment is different (see arguments above). Thus, this new treatment strategy is applicable to this list of diseases. Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 11 and 40 to 42, in view of Document **D1**, **D3, D4** and **D7** be withdrawn.

- Concerning claims 12 to 16 and 43 to 47, the Examiner considers that each documents D1 to D7 discloses PDT-therapy with identical rhodamine derivatives for use in the treatment of at least one of the cancers defined in said claims. The Applicants wish to point out to the Examiner's attention that this represents new usage of these different rhodamine derivatives.

  Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 12 to 16 and 43 to 47, in view of Documents **D1** to **D7** be withdrawn.

- Concerning claims 18 to 27 and 29 to 31, the Examiner considers that document D1 discloses a vaccine. The Applicants wish to point out to the Examiner's attention that the subject

matter described in these claims differs from what is disclosed in D1 for the reasons already pointed out hereinabove.

Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 18 to 27 and 29 to 31, in view of Document **D1** be withdrawn.

Therefore, in view of the aforesaid remarks and arguments, it is respectfully requested that the rejections made in paragraph V2 be withdrawn. **In paragraphs V-3 (supplemental box 2)**, the Examiner motivates his rejections as follows:

- Concerning claims 8, 28 and 39, the Examiner considers that documents **D1** to **D4** teach a subject matter that is essentially identical to what is claimed in said claims, that is infection results in Chagas'disease. In this regard, the Examiner specifies that this disease is known to be a result of contact with the parasite Trypanosoma cruze, which may have an intracellular component. Since this would effectively "activate" the cells similar to other infectious agents, the Examiner considers that it would have been obvious to a person skilled in the art (in the light of **D1**, for instance) to apply this medicament of these claims for this purpose.

  The Applicants wish to point out to the Examiner's attention that in D1 to D4, PDT is used to kill disease cells. Those skilled in the art would then try to eliminate the by-products of the destruction by PDT by washing the cells or other approaches before infusing the cells into the patient. The cells infused to the patients would not be infected. It is also likely that cells that are infected would be activated. Thus, one would logically think that cells activated by the infection will be removed by the PDT process.

  However, the Examiner will note that the present patent rather focuses on preserving dying cells or products released into the supernatant by cells that are PDT treated. What would normally be thrown away is now considered the active ingredient.

  Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 8, 28 and 39, in view of Documents **D1** to **D4** be withdrawn.

- Concerning claims 17 and 48, the Examiner considers that in the light of the teaching of documents **D1** to **D4**, especially he is of the opinion that antigen presenting cells are commonly known to help initiate immune response to T cells, it would have been obvious to combine these cells with PDT-treated cells, such that they would be in close proximity with the released antigens and it would be expected that the immune response would be facilitated.

  The Applicants wish to point out to the Examiner's attention that they agree that it is known that antigen presenting cells can be used in conjunction with immunizing antigen. However, the Examiner will note (same argument as above): the dead cells, debris from dead cells and

products generated from cells treated by PDT were previously washed away from the graft and not infused into the patient. If one considers that the beneficial effect is obtained by infusing normal cells, and changing the balance in favor of normal cells over diseased cells, then one would not think of adding dendritic cells to the process.

Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 17 and 48, in view of Documents **D1** to **D4** be withdrawn.

- Concerning claims 18 to 22, the Examiner considers that in the light of the teaching of documents **D2** to **D4**, there is a lack of inventive step because these claims are essentially identical to the subject-mater of claims 1, 14 and 15 except that they pertain to an identical medicament as defined in claim 1 in combination with a pharmaceutically acceptable carrier. The Examiner point out that the addition of a carrier is well known in the art.

  The Applicants wish to point out to the Examiner's attention that the combination with a carrier in D2 to D4 is oriented toward a stabilizer. However, the Examiner will note that in the present patent application, the carrier would be a substance to promote the immunization process.

  Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 18 to 22, in view of Documents **D1** to **D4** be withdrawn.

- Concerning claims 23 to 25, the Examiner considers that in the light of the teaching of document **D2**, there is a lack of inventive ingenuity.

  The Applicants wish to point out to the Examiner's attention that even though targeted diseases are the same, the treatment approach by itself is different as described above.

  Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 23 to 25, in view of Document **D2** be withdrawn.

- Concerning claims 21 to 31, the Examiner considers that in the light of the teaching of documents **D3** and **D4**, there is a lack of inventive ingenuity.

  The Applicants wish to point out to the Examiner's attention that even though targeted diseases are the same, the treatment approach by itself is different as described above.

  Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 21 to 31, in view of Documents **D3** and **D4** be withdrawn. Therefore, in view of the foregoing it is respectfully requested that the rejection made in paragraphs V-3 (supplemental box 2) be withdrawn.

Section VIII

In paragraph VIII, the Examiner raised numerous formals objections against the disclosure and the claims.

More particularly, the Applicant has noted the objection raised by the Examiner against claims 13 and 44 under Articles 5 and 6 of the PCT and requesting clarification with respect to the perfusion. In this regard, the Examiner will note that the cells can be collected from the patient into a catheter, treated in a PDT machine and immediately injected into the patient, without washing or any other step. In this instance, the patient is in continuous contact with the instrument through a tube and the cells are infused into the patient for as long as the duration of the treatment.

Also, the Examiner will note that it is possible that these cells are treated several times by PDT since they are reinjected into the patient after treatment. Indeed, the treatment is a continuous process where cells are constantly collected through the needle inserted in the vein and reinfused into another vein of the patient. Alternatively, the cells could be collected, treated ex vivo and reinfused immediately after light exposure, without any washing or removal of dead cells or supernatant. Thus, the treatment is also mediated by infusion of the treated diseased cells. This approach treats only a fraction of the circulating blood at a time. The treatment is therefore ex vivo, however the treatment again represents the infusion of the cells modified by the treatment.

Therefore, in view of the foregoing, it is respectfully requested that the rejection made by the Examiner against claims to 13 and 44, in view of sections 5 and 6 of the PCT be withdrawn.

The Applicants have noted the objection raised by the Examiner against the use of the expression "surpernatant". However, the Applicants do not agree with the suggestion made by the Examiner to replace the term "surpernatant" by the term "lysate", both terms not being equivalent. Also, the term "surpernatant" is quite well understand by skilled workman and do not necessitate any additional comments.

All the other objections raised by the Examiner have been fully overcome according to Examiner's proposals. Replacement pages are hereby submitted.

It is believed that the Examiner should be in a position to establish a favourable IPER with respect to all of the claims, but if some matters are still considered outstanding, then a further Written Opinion is requested.

Respectfully,

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MB/lcc

Encs. : - Pages 2 and 16 of the disclosure;
- Claims 1 to 49.